

Squirreling away at Parkinson's

Thomas S. May, freelance writer

Some animals manage to survive the long, cold winter months by entering a state of suspended animation called hibernation. Hibernation protects them from starving to death when there is a lack of food in their environment, and new research suggests that a compound that triggers hibernation in ground squirrels can also protect brain cells from the lack of oxygen following a stroke.

There is also evidence that the same chemical, [D-al²,D-leU⁵]enkephalin (DADLE), can also protect neurons under other adverse conditions. For example, DADLE appears able to minimize neuronal damage caused by toxic substances, and it can also enhance the viability of foetal nerve cells during transplantation. As a result, this delta opioid peptide might some day be used to help prevent – and perhaps cure – various neurodegenerative disorders, such as Parkinson's disease (PD), researchers suggest.

According to Cesario Borlongan, Associate Professor at the Department of Neurology and Institute of Molecular Medicine at Medical College of Georgia (<http://www.mcg.edu/>), hibernation is an evolutionary extension of sleep, and there is some evidence that a lack of sleep could be a predisposing or exacerbating factor

for several neurological disorders in humans. Therefore, he says, it seems logical to study the role of hibernation or 'hibernation-like states' in neurological disorders.

Protecting cells everywhere

'We have conducted both *in vitro* and *in vivo* studies demonstrating that DADLE protects neurons from cell death', Borlongan said.

In one experiment, a group of rats had their middle cerebral artery temporarily clamped to induce cerebral ischemia in an experimental model of stroke. The investigators found that animals that had been injected with DADLE experienced significantly less ischemia-induced brain damage than animals that had not been pretreated with the substance [1] (Fig. 1).

Earlier studies, in which researchers introduced various neurotoxic or cytotoxic chemicals into the brains of experimental animals, yielded similar results. Namely, DADLE effectively reduced cell death induced by the administration of methamphetamine [2] and 6-hydroxydopamine [3], both of which are potent neurotoxins.

DADLE also appears to enhance the (*in vitro*) survival of nerve cells harvested from developing foetuses, and this has important implications for the treatment of PD in the future, Borlongan says. In a study published last year in the journal *Cell Transplantation*, he and his colleagues at the National Institute of Drug Abuse in the USA (NIDA; <http://www.nida.nih.gov/>) tested the viability of dopaminergic neurons that had been removed from 14-day-old rat foetuses [4]. The results

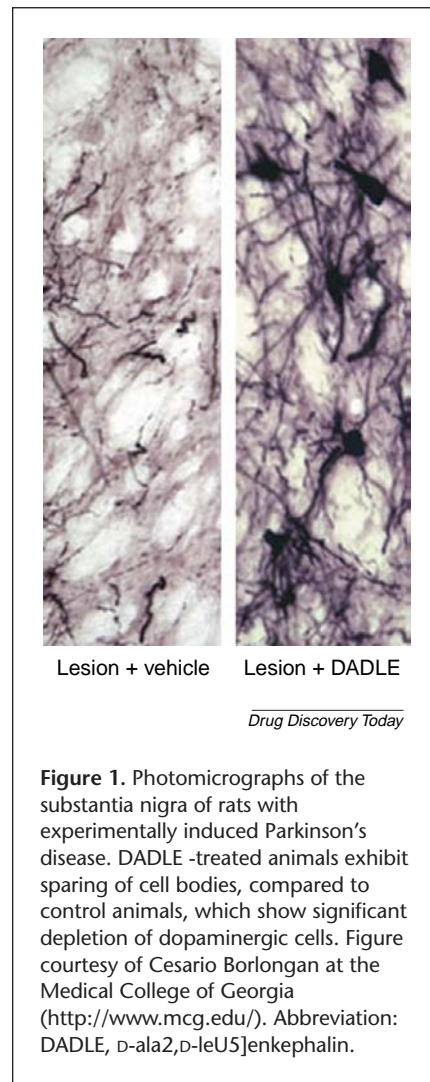


Figure 1. Photomicrographs of the substantia nigra of rats with experimentally induced Parkinson's disease. DADLE -treated animals exhibit sparing of cell bodies, compared to control animals, which show significant depletion of dopaminergic cells. Figure courtesy of Cesario Borlongan at the Medical College of Georgia (<http://www.mcg.edu/>). Abbreviation: DADLE, D-al²,D-leU⁵]enkephalin.

showed that a significantly larger number (85% compared with 60%) of the cells survived after three days if they were stored in a solution containing DADLE.

Prospects for PD

PD develops when a large number of dopaminergic neurons are destroyed in a specific area of the brain, and replacing these cells with foetal nerve cells is one of the most promising



treatment options currently being explored. However, one of the major problems in neural transplantation is finding an ample supply of viable cells, Borlongan points out.

The demonstration that DADLE produces extended survival of cells has direct clinical application for transplantation therapy, he claims. 'With DADLE being able to prolong survival of nerve cells, pooling of viable cells is possible', he said.

Furthermore, when (in an extension of the above study) the harvested foetal cells were transplanted into the brains of parkinsonian rats, the DADLE-treated cells not only survived better than the non-treated cells, but they also promoted enhanced behavioral recovery in the transplanted animals. 'These results suggest that DADLE should be considered as an adjunctive agent for neural transplantation therapy in Parkinson's disease', the researchers concluded.

How does it work?

Although no one knows exactly how this compound exerts its neuroprotective effects, DADLE appears to be a powerful antioxidant,

and this might partially explain why it protects nerve cells.

According to Borlongan, 'the aberrant accumulation of free radicals has been documented in Parkinson's disease and other neurological disorders'. Therefore, he argues that the most plausible explanation for the neuroprotective effects of DADLE is 'via its free radical scavenging property'.

Tsung-Ping Su, Chief of the Cellular Pathobiology Unit at NIDA, agrees with Borlongan, but thinks that there are other processes involved as well: 'DADLE can also block the translocation of a Bax protein from the cytosol into the mitochondria, the consequence of which is to cause a release of cytochrome c that can activate all sorts of caspase enzymes to kill cells', he explained.

Looking ahead

Whatever the mechanism behind it, there is convincing evidence that DADLE is an effective neuroprotector, according to Su. Therefore, he suggests that it could be used as a therapeutic agent for various neurological and aging-related diseases in the future.

Su admits that several things must happen before clinical studies involving humans can take place. First, the bioavailability and biosafety of DADLE must be tested after intravenous administration in animals, he contends. However, if all of the initial tests are successful this unique substance, which triggers hibernation in squirrels, might one day be used to prevent or treat several neurological diseases, including stroke and PD, he says.

References

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- 2 Tsao, L. *et al.* (1999) Reversal by [D-al², D-leu⁵]enkephalin of the dopamine transporter loss caused by methamphetamine. *Eur. J. Pharmacol.* 372, R5–R7
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Mistletoe compound enters clinical trials

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For many years, mistletoe extract has been popular with cancer patients, but not with scientists. Now, there is a drug in clinical trials that contains a recombinant version of the extract's main active ingredient [1,2].

Under the mistletoe

Extract from the mistletoe plant (*Viscum album*) is widely used as an

alternative complementary therapy, especially in German-speaking countries (this is a result of the proposition, by Austrian Rudolf Steiner in the early 1920s, that mistletoe could be used as a therapeutic agent for the treatment of cancer). However, scientists have traditionally been skeptical about this treatment approach. So is Patrick Schöffski,

a hematologist at Hannover Medical School (<http://www.mh-hannover.de>): 'Natural extracts have the disadvantage that they contain many ingredients at varying concentrations. I am very excited to have the chance to study one ingredient, genetically engineered mistletoe lectin 1, in conventional clinical studies.'